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Sleep Deprivation Affects Somatosensory Cortex Excitability as Tested Through Median Nerve Stimulation

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ABSTRACT

Background: Changes of cortical excitability after sleep deprivation (SD) in humans have been investigated mostly in motor cortex, while there is little empirical evidence concerning somatosensory cortex, and its plastic changes across SD.
Objective: To assess excitability of primary somatosensory cortex (S1) and EEG voltage topographical characteristics associated with somatosensory evoked potentials (SEPs) during SD.
Methods: Across 41 h of SD, 16 healthy subjects participated in 4 experimental sessions (11.00 a.m. and 11.00 p.m. of the 1st and 2nd day) with: a) subjective sleepiness ratings; b) EEG recordings; c) SEPs recordings; d) behavioral vigilance responses.
Results: A clear enhancement of cortical excitability after SD was indexed by: (a) an amplitude increase of different SEPs component in S1; (b) higher voltage in occipital (around 35–43 ms) and fronto-central areas (around 47–62 ms). Circadian fluctuations did not affect cortical excitability. Voltage changes in S1 were strongly related with post-SD fluctuations of subjective and behavioral sleepiness.
Conclusions: Sleep may have a role in keeping cortical excitability at optimal (namely below potentially dangerous) levels for the human brain, rebalancing progressive changes in cortical responsiveness to incoming inputs occurred during time spent awake. On the other hand, higher level of cortical responsiveness after sleep loss may be one of the mechanisms accounting for post-SD alterations in vigilance and behavior.

Introduction

Neurobehavioral effects of sleep deprivation (SD) on human alertness and performance are well established. Subjective and objective measures of sleepiness point to reduced alertness [1] and impaired performance on both simple and complex tasks, as indexed by tests of reaction time, vigilance, attention [2] and executive functions [3]. The degrading effects of SD on alertness and cognitive performance are associated to alterations in the underlying brain physiology, as measured by functional Magnetic Resonance Imaging (fMRI) mostly showing increased activations, possibly related to task-specific changes in the brain response. These effects however depend on (a) the magnitude of global decline in general alertness and attention [4], (b) the degree to which the specific cognitive function involves specific neural

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networks [5], and (c) the extent to which a specific cognitive process can draw upon associated cortical regions for compensatory support [6,7].

On the other hand, the magnitude of cortical decline in general alertness is better described by electroencephalographic (EEG) measures obtained during resting states showing that slow EEG frequencies up to 7 Hz progressively increase during prolonged wakefulness, with larger magnitude on the frontal regions [8,9]. However, resting EEG describes changes of spontaneous cortical activity, and the deactivations expressed by the increased slow-frequency activity do not necessarily contradict the functional activations shown by fMRI measures. Indeed, neuroimaging studies and resting EEG studies do not *directly* measure changes of cortical excitability as a consequence of SD.

Cortical excitability of human motor cortex has been studied through transcranial magnetic stimulation (TMS), a noninvasive tool enabling the stimulation of cortical neurons [10]. Changes in cortical TMS-evoked responses have been observed in human motor cortex after different manipulations of time spent in wakefulness [8,11–13], and their extent is correlated to the concomitant changes in spontaneous slow-frequency EEG activity [8]. Notably, some studies have found no significant changes in motor cortical excitability after SD [14,15], but this result has been ascribed to a lack of statistical power due to the small sample sizes [13] and/or to the confounding of circadian factors [8]. The excitability of the supplementary motor cortex, measured as the EEG response to TMS, progressively increases with time awake, from morning to evening and after one night of total SD, with a return to baseline after one night of recovery sleep [16]. SD also increases cortical excitability in epilepsy, probably due to a reduction of intracortical inhibition [17] and is the reason why it is still widely used as an activation test in clinical electroencephalography [18]. However, none of these studies has been designed to evaluate the effect of SD on the excitability of cortical areas different from the primary and associative motor cortices. Since several studies [19,20] have found different modulatory effects of sleep on Somatosensory Evoked Potentials (SEPs), they may be used to investigate the effects of SD on the excitability of the somatosensory cortex. The only study about the effects of SD on somatosensory cortical excitability showed an increased amplitude of early SEPs components with time awake, but did not account for the influence of circadian fluctuations [21]. Moreover, results from a very recent experiment in rats [22] suggest a higher increase of responsiveness in parietal than in frontal areas after SD. Conversely, Chauvette and co-workers [23] found in cats an enhancement of SEPs after a slow-wave sleep episode, as compared to previous wake. For this reason, we have assessed cortical excitability of the somatosensory cortex by measuring cortical responses to median nerve stimulation across 41 h of prolonged wakefulness. As a final reason for studying the parietal cortex, it should be mentioned that it revealed clear plastic changes increasing [24] or decreasing [25] its local need triggered by specific learning tasks. In other words, it seems very responsive to manipulations of diurnal physiology.

The aims of the current study are:

1. to evaluate the cortical responsiveness during a period of prolonged wakefulness, by assessing both changes in the early components of SEPs and changes in scalp distributions of voltages; we hypothesize an increase of cortical excitability after SD;
2. to control for the effects of circadian fluctuations, through four different sessions scheduled at the same time of the day; we hypothesize that circadian effects – if present – should be of smaller extent compared to those induced by SD, resembling the well documented changes in resting EEG activity during prolonged wakefulness [8,26].

Material and methods

Subjects

Sixteen healthy male volunteers took part in the experiment (mean age ± SE = 23.3 ± 0.64 years). All subjects self-reported as right-handed and without history of central or peripheral neurological impairment. Exclusion criteria were: brain injury, alcohol abuse, diabetes, drug addiction, and contra-indications to TMS [27]. Inclusion criteria were: normal sleep duration (habitual sleep time: 24.00–8.00 ± 1 h) and schedule, no daytime nap habits, no excessive daytime sleepiness, no other sleep, medical or psychiatric disorder, as assessed by a one-week (mean ± SE = 7 ± 0.3 days) sleep log, the score on the Italian version of the Pittsburgh Sleep Quality Index (PSQI – [28]), and a clinical interview. Participants were required to avoid napping; actigraphic recordings (AMI Mini motion logger) were collected for about one week (mean ± SE = 7 ± 0.3 days) before the beginning of the experimental procedure to control subjects' compliance.

All subjects gave their written informed consent. The study was approved by the Institutional Ethics Committee of the Department of Psychology of the University of Rome "Sapienza", and was conducted in accordance with the Declaration of Helsinki.

Procedure

Study design

The main aim of the experiment was to determine changes of cortical excitability as a function of the time spent awake. Figure 1 shows the timeline diagram of the experimental protocol. On the morning of the experiment participants woke up on average at 7.00 a.m. (mean ± SE = 6.54 ± 0.13 a.m. based on sleep log), and arrived at the laboratory at 9.00 a.m. for the electrodes montage. Experimental procedure started at 11.00 a.m. Subjects were evaluated in four different sessions carried out at the same time (11.00 a.m. and 11.00 p.m.) of the first and second day. Each session included: a) subjective sleepiness recordings; b) EEG recordings (5 min eyes-open condition); c) SEPs recordings; d) behavioral sleepiness recordings. We used this fixed sequence due to the relatively small sample size and to the main focus on electrophysiological measures. According with the aims of a corollary experiment, after SEPs recordings subjects were exposed to a paired associative stimulation (PAS) protocol [29,30], combining a single electric stimulus delivered at specific time intervals to a peripheral nerve with a single TMS pulse on contralateral S1, aimed to evaluate SD-dependent alterations in long-term potentiation (LTP) mechanisms [31]. Results on the effects of PAS after SD will be reported elsewhere.

During the experimental sessions, participants were seated on a comfortable chair in a soundproof, electrically shielded room. They were required to keep their right arm completely relaxed during the entire experimental session.

The 41 h schedule of SD ended at midnight on the second day (see Supplementary Material for the rules of the SD protocol).

Subjective sleepiness

Self-rated sleepiness was measured every 2 h (starting at 11.00 a.m. of the first day) by the Karolinska Sleepiness Scale (KSS – [32]) and the Visual Analog Scale for Global Vigor (VAS – [33]). The KSS is a 9 points rating scale, ranging between "very alert" (1) and "very sleepy, fighting sleep" (9), while the VAS is a paper-and-pencil measure of subjective alertness which combines the scores on four continuous 10 cm scales (alert, sleepy, weary and effort) to obtain a Global Vigor score between 0 and 40 cm. According to the aims of the current study and to the analyses on electrophysiological and

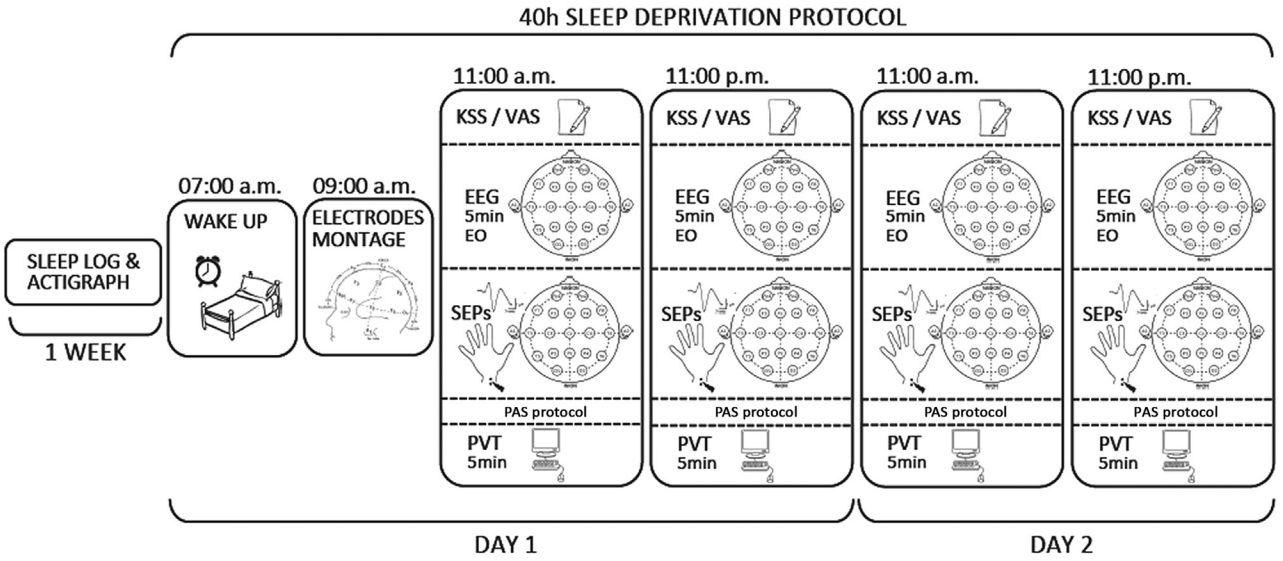

Figure 1. Timeline diagram of the experimental protocol. During the week preceding the beginning of the sleep deprivation period, subjects were monitored by actigraphic recording and sleep log. On the morning of the experiment subjects on average woke up at 7.00 a.m. (mean ± SE = 6.54 ± 0.13 based on sleep log) and went in the laboratory at 9.00 a.m. for the electrodes montage. Experimental procedure started at 11.00 a.m. Subjects were evaluated in four different sessions carried out at the same time (11.00 a.m. and 11.00 p.m.) of the first and second day. Each session was conducted in the following sequence: a) subjective sleepiness recordings (Karolinska Sleepiness Scale and Visual Analog Scale for Global Vigor); b) EEG recordings (5 min eyes-open condition); c) SEPs recordings; d) behavioral sleepiness recordings (Psychomotor Vigilance Task). After SEPs recordings subjects were exposed to a paired associative stimulation (PAS) protocol (results on the effects of PAS after SD will be reported elsewhere). The 41 h schedule of sleep deprivation ended at midnight on the second day.

behavioral measures, only data collected in correspondence of the 4 SEPs experimental sessions (at 11.00 a.m. and 11.00 p.m. of first and second day) will be reported.

Electrical somatosensory stimulation

Electrical nerve stimulation was performed with a bipolar electrode (cathode proximal), connected to an electromyography (MYto, EBNeuro, Italy). The stimulating electrode was placed on the right median nerve (MN) at the level of the wrist (cathode proximal). MN stimulation was performed using a pulse with a 200 μs width at a frequency of 3 Hz and a stimulation intensity of ~300% of the individual perceptual threshold [34]. The hand representation at primary somatosensory cortex ("somatosensory hot-spot") was marked 2 cm posterior to C3 position, corresponding to Cp3 [34]. The responses to 500 electric stimuli were recorded and averaged. See Supplementary Material for further information.

Recordings

An Esaote Biomedica VEGA 24 polygraph was used for EEG polygraphic recordings. EEG signals were recorded from 20 sites using Ag/AgCl sintered ring electrodes mounted on an elastic cap (EasyCap GmbH, Herrsching, Germany). The nineteen unipolar EEG derivations of the international 10–20 system (Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, P3, P4, Pz, T3, T4, T5, T6, O1, O2) were recorded from scalp electrodes with averaged earlobes reference (A1, A2), with the addition of an electrode over the somatosensory hot-spot (Cp3). Horizontal eye movements were detected by recording electrooculograms (EOGs) in order to monitor subject behavior online and reject, off-line, trials with ocular artefacts. Electromyogram (EMG) was recorded by two submental electrodes. During SEPs recordings EEG, EOG and EMG signals were acquired at a sampling rate of 5 kHz and band-pass filtered at 0.03–1500 Hz. The skin-electrode impedance was kept below 5 kΩ. EEG, EOG and EMG electrodes were not removed after any recording session, and impedances were checked before the beginning of each session. Some information about resting EEG data is reported as Supplementary Material.

Surface EMG activity was recorded from the right APB muscle with the active electrode mounted on the belly muscle and the reference electrode placed over the base of the metacarpophalangeal joint of the thumb. Active and reference electrodes were removed after every experimental session and their positions were marked with a soft-tip pen. Impedances were checked before the beginning of each session. During SEPs recordings subjects were asked to keep their eyes open and to fixate a point on the wall.

Psychomotor vigilance task

After every SEPs experimental session a 5 min version of the Psychomotor Vigilance Task (PVT – [35]) was administered as a behavioral measure of sleepiness. The PVT is a well-known and reliable computerized task that requires sustained attention to detect randomly occurring stimuli [35]. The PVT is free of aptitude and learning effects and is sensitive to performance variations due to sleepiness [36]. Median reaction times (RTs) were measured.

Data and statistical analysis

SEPs early components analysis

The optimal site for SEPs components analysis was the Cp3 electrode; we also considered the adjacent C3 and P3 electrodes. All the collected data were epoched off-line between −32 and +88 ms relative to the MN stimulation. Epochs containing artefacts were rejected. For each recording, baseline was computed by averaging all the samples between −30 and −4 ms. Measurement windows for the considered early SEPs components (P14, N20, P25, N30, P40) were determined by visually inspecting the single SEPs recordings (see Supplemental Material). A two-way repeated measures design analysis of variance (ANOVA), Day (pre-SD vs. post-SD) × Time of Day (11.00 a.m. vs. 11.00 p.m.) was carried out for each SEPs component measured at the Cp3, C3 and P3 electrodes. Because of the large number of ANOVAs (15 in total) performed to investigate changes in several early SEPs components from different scalp derivations, a correction for alpha inflation was applied through the

False Discovery Rate [37] (FDR; for a detailed explanation, see Supplemental Material).

Topography of SEPs

The detection of early SEPs components after MN stimulation can be very difficult at scalp locations far from S1: not all the components are reliably identifiable at all the cortical sites. For this reason, the analysis of SEPs scalp topography after SD was performed on the EEG voltages recorded in a time window including all the SEPs components described in the 'SEPs early components analysis' section, rather than on the SEPs early components. Hence, for each cortical derivation, all the SEPs recordings were transformed in z-scores within each subject (considering all samples between −30 and +70 ms), sequenced into 1 ms epochs from 10 to 69 ms, and then averaged across subjects. Statistical comparison between pre- and post-SD SEPs voltages at all the time points were carried out for every scalp location by paired two-tailed *t*-test. Because of the large number of comparisons, the FDR was applied to correct for alpha inflation.

Subjective sleepiness

Self-rated measures of sleepiness (KSS and VAS) were submitted to a two-way repeated measures ANOVA design, Day (Pre-SD vs. Post-SD) × Time of Day (11.00 a.m. vs. 11.00 p.m.).

Psychomotor vigilance task

Changes in PVT performance as a consequence of SD were measured by means of two-way repeated measures ANOVA design, Day (Pre-SD vs. Post-SD) × Time of Day (11.00 a.m. vs. 11.00 p.m.), carried out on the median RT.

Correlation between SEPs, behavioral and self-rated changes after sleep deprivation

In case of significant changes of SEPs topography as a consequence of sleep deprivation, changes of voltage have been windowed to the time bin exhibiting the largest voltage increase after SD (ΔSEPs), and have been correlated to changes of both behavioral (ΔPVT) and subjective (ΔKSS and ΔVAS) measures of sleepiness, by Spearman's rank correlations computed for each scalp location. To correct for multiple comparisons, the FDR have been applied.

Results

Early components of SEPs

Figure 2 shows the grand average of SEPs recorded at Cp3 location in the 4 experimental sessions. The Day × Time of Day ANOVAs (main effects and interactions reported in Table 1) show a significant (FDR $q \leq 0.01$; $P \leq 0.05$, corresponds to an $F \geq 4.41$) main effect of Day at Cp3 for the P14, P25 and P40 components, with an amplitude increase of these components after SD (Fig. 3A). The same effect was observed over C3 site (Fig. 3B) for the P14, P25 and P40 components and over P3 (Fig. 3C) for the P25 and N30 components. No significant Time of Day main effect or interaction were observed for these scalp locations. Control measures on the reliability of SEPs data are reported as Supplementary Material.

In summary, SD induced an amplitude increase in different early SEPs components (P14, P25 and P40 at Cp3 and C3; P25 and N30 at P3) without any influence of circadian factors.

Scalp distribution of voltages changes associated to SEPs

Since the lack of significant Time of Day main effect and Day × Time of Day interaction, for each day we collapsed voltage values at different times (morning and evening values). Then, for the subsequent analyses on the voltages scalp distribution associated to SEPs, we compared the averaged voltage of the SEPs recorded during the first day (pre-SD) with the average voltage of the SEPs recorded during the second day (post-SD). Supplementary Figs. S1 and S2 show the topographic distribution of EEG voltage associated to SEPs pre- and post-SD, respectively. Figure 4 depicts

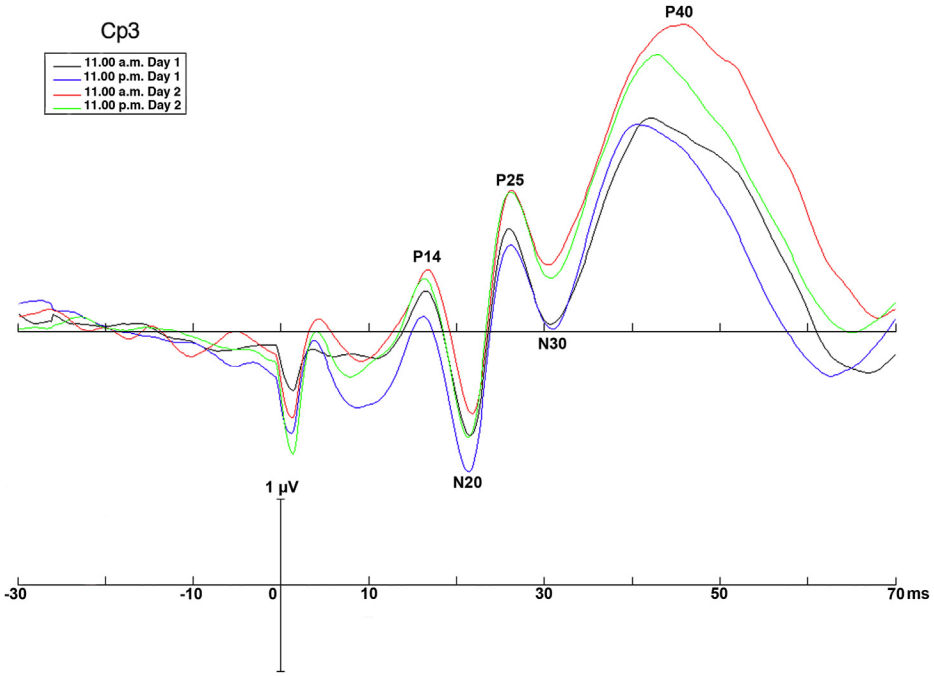

Figure 2. Grand average waveforms of somatosensory evoked potentials (SEPs) following right median nerve stimulation during the four experimental sessions at Cp3 of 16 male subjects.

Table 1
Main effects and interactions of the Day (D) × Time of Day (T) ANOVAs on early somatosensory evoked potentials (SEPs) components amplitude (P14, N20, P25, N30, P40) in the scalp locations Cp3, C3, P3. Significant effects are indicated in bold.

	$F_{(1,15)}$			P		
	Cp3	C3	P3	Cp3	C3	P3
P14 D	**4.94**	**6.88**	1.10	**0.04**	**0.02**	0.31
P14 T	1.76	2.39	0.49	0.20	0.14	0.49
P14 D × T	0.30	0.004	0.16	0.59	0.95	0.70
N20 D	1.45	2.18	0.37	0.25	0.16	0.55
N20 T	3.87	3.38	0.73	0.07	0.09	0.41
N20 D × T	0.39	0.10	0.34	0.54	0.76	0.57
P25 D	**6.97**	**6.62**	**4.41**	**0.02**	**0.02**	**0.05**
P25 T	0.58	1.88	0.13	0.46	0.19	0.72
P25 D × T	0.02	0.02	0.009	0.90	0.90	0.93
N30 D	2.77	1.06	**5.43**	0.12	0.32	**0.03**
N30 T	0.37	1.54	0.006	0.55	0.23	0.94
N30 D × T	0.004	0.03	0.02	0.95	0.87	0.88
P40 D	**6.14**	**13.48**	3.56	**0.03**	**0.002**	0.08
P40 T	0.80	2.39	0.08	0.39	0.14	0.78
P40 D × T	1.07	0.13	0.63	0.32	0.72	0.44

the statistical maps (*t*-values maps) of the comparisons between pre- and post-SD SEPs voltages in the time window 10–69 ms. Significant changes (FDR $q \leq 0.05$; two-tailed $P \leq 0.003$ corresponds to $t \geq 3.58$), in terms of a voltage increase after SD, were found in correspondence of the left occipital site (O1 at 35–43 ms) and of the fronto-central areas (C3 at 56–60 ms, Cz at 47–62 ms, F3 at 51–62 ms, F4 at 49 ms and Fz at 47–62 ms). The maximum voltage increase was observed in Fz at 54 ms.

Subjective sleepiness

Subjects were significantly more sleepy after SD (Fig. 5A) as indicated by the presence of a significant main effect of Day on the KSS scores ($F_{1,15} = 26.69$; $P = 0.0001$). There was also a significant main effect of Time of Day ($F_{1,15} = 6.75$; $P = 0.02$) with higher KSS scores in the morning (11.00 a.m. = 6.12 SE = ±0.39; 11.00 p.m. = 5.37 SE = ±0.35), but it was characterized by a small effect size ($\eta^2 = 0.04$). The Day × Time of Day interaction was not significant.

A significant main effect of Day on the VAS scores was also observed ($F_{1,15} = 48.59$; $P = 0.000005$), with higher VAS scores after SD, indicating that subjects were also less alert after SD (Fig. 5B). The Time of Day (11.00 a.m. = 19.96 SE = ±1.30; 11.00 p.m. = 21.59 SE = ±1.17; $F_{1,15} = 4.38$; $P = 0.05$) main effect and the Day × Time of Day interaction ($F_{1,15} = 4.71$; $P = 0.05$) were marginally significant.

Psychomotor vigilance task

As detailed in Fig. 5C, PVT performance was significantly worse (longer RTs) after SD ($F_{1,15} = 12.16$; $P = 0.003$). No significant Time of Day effect or interaction were observed ($F < 2$).

Correlation between SEPs, behavioral and self-rated changes after sleep deprivation

Since results show that both behavioral and subjective measures of sleepiness, and SEPs voltage topography were influenced by SD (pre-SD vs. post-SD comparisons), with only marginally significant Time of Day and interaction effects on VAS measure and a main effect of Time of Day on KSS measure with a small effect size, we examined the existence of a relationship between post-SD changes in SEPs topography and those in behavioral (PVT) and self-rated (KSS and VAS) measures of sleepiness after SD. Changes of SEPs voltage at 54 ms (i.e., the time bin exhibiting the largest voltage increase after SD) were averaged across the morning and evening conditions (ΔSEPs). Similarly, averaged measures for the Day 1 and 2 were considered with respect to KSS (ΔKSS), VAS (ΔVAS) and PVT (ΔPVT) measures. The topographical distribution of the correlation coefficients is illustrated in Fig. 6. Significant positive correlations (FDR $q \leq 0.03$; $P \leq 0.05$ corresponds to $\rho \geq 0.51$) were found between ΔSEPs 54 ms and ΔKSS (Cp3, F3, P3, Pz), ΔVAS (C3, C4, Cp3, Cz, P3, P4, Pz, T3, T5) and ΔPVT (P3, T5). The highest correlations were observed in correspondence of (and near to) the S1 area.

Discussion

The main aim of the present study was to assess the effects of 41 h of SD on cortical excitability, in terms of changes in early SEPs components in S1 cortex and modifications in voltages scalp distribution after MN stimulation. To the best of our knowledge, this is the first study aimed at estimating changes in voltage topography associated to SEPs during prolonged wakefulness. Results show a clear amplitude increase of different SEPs components over S1 after sleep loss, and an increment of voltage in fronto-central and occipital areas in a time-window that substantially overlap the time range used for the detection of the P40 component. Both findings point to a higher level of cortical responsiveness after prolonged wakefulness. Changes in the scalp distribution of voltages were positively correlated with subjective and behavioral measures of sleepiness, especially in the S1 area.

Sleep deprivation-induced amplitude increase of early SEPs components

As expected, the amplitude of different SEPs components increased after sleep loss, indicating an enhancement of cortical excitability. A post-SD amplitude increase of the P14 was observed in the Cp3 and C3 scalp locations. Previous studies showed that the P14 has a subcortical origin, probably located in the brainstem tracts of lemniscal system [38]. The amplitude of the P25 increased at all of the three scalp locations taken into account (Cp3, C3 and P3) and this may reflect a specific effect of SD on S1, since this component is generated in the posterior bank of the central sulcus

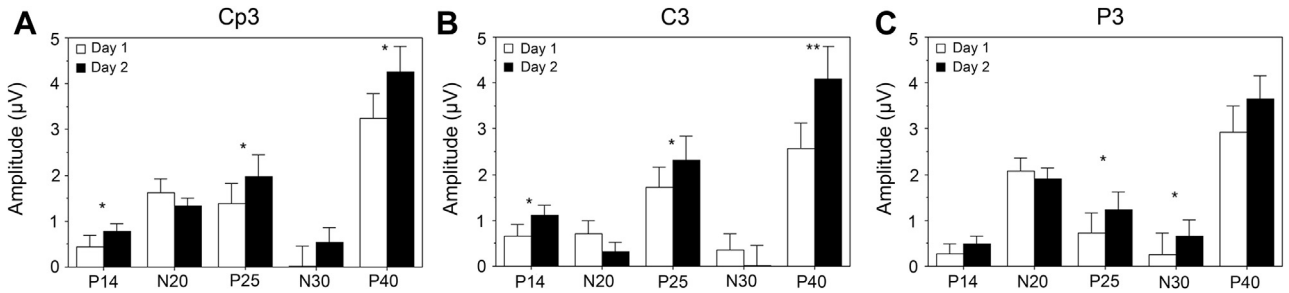

Figure 3. Mean amplitude (expressed in μV) of the somatosensory evoked potentials (SEPs) components P14, N20, P25, N30 and P40 in 16 male subjects during the day before (white bars) and after (black bars) sleep deprivation (*$P < 0.05$, **$P < 0.005$), in the scalp derivations Cp3 (A), C3 (B) and P3 (C). Error bars represent the standard errors.

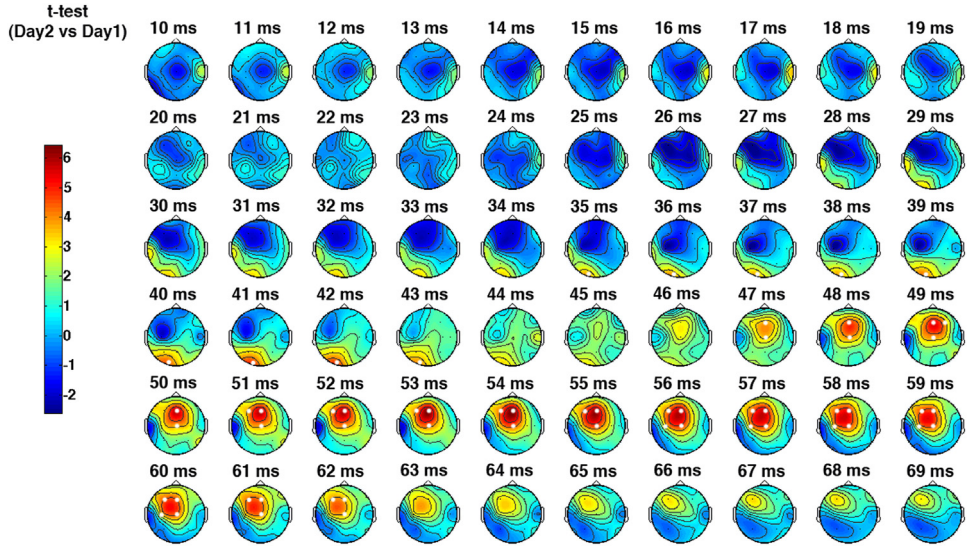

Figure 4. Statistical maps (*t*-values maps) of the comparison between pre- and post-sleep deprivation (SD) somatosensory evoked potentials (SEPs) voltages in the time window 10–69 ms with time-bins of 1 ms. Values are expressed in terms of *t*-values ($n = 16$): positive t-values indicate a prevalence of the post-SD over the pre-SD voltage and vice-versa. The two-tailed level of significance after False Discovery Rate (FDR) correction ($q \leq 0.05$; $P \leq 0.003$) corresponds to $t \geq 3.58$. The maps are based on 20 derivations (electrode positions indicated by dots). Values are color-coded and plotted at the corresponding position on the planar projection of the hemispheric scalp model. Values between electrodes were interpolated (biharmonic spline interpolation). Filled white circles indicate the electrodes with significant difference.

[38,39]. The N30 shows an amplitude increment only in the P3 derivation. A parietal negative component around 30 ms seems to involve generators in superficial area 1 [40] and is thought to represent the arrival of the sensory volley at the somatosensory cortex [41]. An amplitude enhancement of the P40 after SD was found at Cp3 and C3. In particular, at the C3 site this component reached the maximal amplitude increase observed in the present study. The main P40 generator would be located in the post-central gyrus, corresponding to the Brodmann area 1 [39]. SD, then, seems to affect the somatosensory information processing at different levels: (a) a subcortical level, when sensory information travels from the brainstem to the thalamus; (b) at a cortical level, when sensory information is processed by S1. These results are partially coherent with the only previous study relative to the effects of sleep loss on early SEPs components [21] that showed, after 24 h of prolonged wakefulness, an amplitude increase of the parietal N20–P24 complex, probably due to potentiation of the P24, and of the frontal P45–N60 complex. Moreover, different studies found an amplitude decrease of SEPs components recorded from scalp derivations placed on the parietal area during sleep, while the frontal components showed an amplitude increase [19] or no significant changes [20], suggesting that both excitatory and inhibitory processes are active during sleep. It is possible that sleep may be necessary to rebalance changes in cortical responsiveness induced during wakefulness and, conversely, sleep loss may lead to an increase in cortical excitability in those areas that need a sleep-related inhibition process. Previous studies showed higher responsiveness in many cortical regions after prolonged wakefulness, as assessed by different methods such as motor evoked potentials (MEPs – [12,13,17]), TMS-evoked EEG responses (TEPs – [16,42]) and event-related potentials during a passive auditory oddball task [43]. Our findings confirm the existence of a cortical responsiveness enhancement after SD, and extend this result to the somatosensory cortex.

The time of day when SEPs were recorded (morning or evening) did not exert any influence on the amplitude of the SEPs components, suggesting that somatosensory cortical excitability is not affected by circadian factors. SEPs recording, then, can be

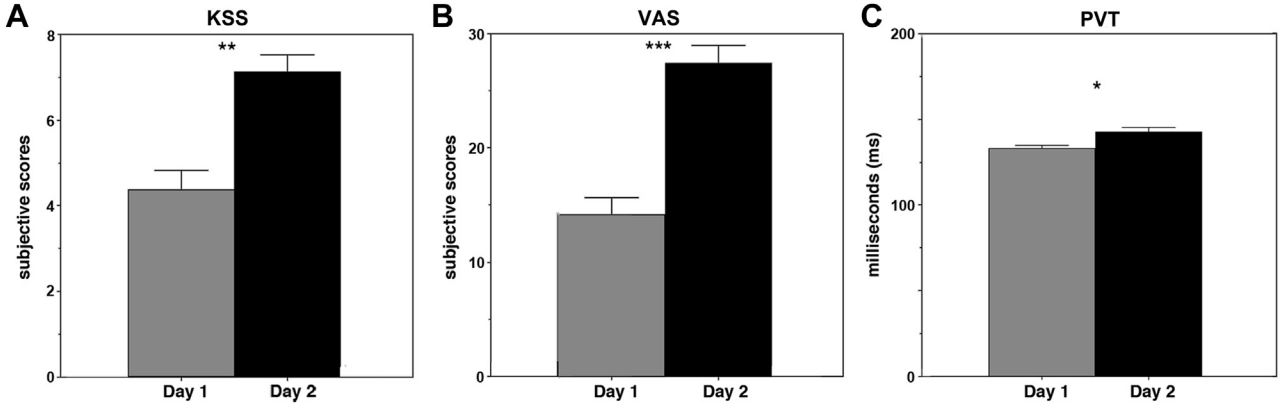

Figure 5. Effect of sleep deprivation (SD) on subjective and behavioral measures of sleepiness in 16 male subjects (*$P < 0.005$, **$P < 0.0005$, ***$P < 0.00001$). (A) Mean Karolinska Sleepiness Scale (KSS) scores during the day before (gray bar) and after (black bar) SD. (B) Mean Visual Analog Scale for Global Vigor (VAS) scores during the day before (gray bar) and after (black bar) SD. (C) Mean time reaction (expressed in ms) at Psychomotor Vigilance Task (PVT) during the day before (gray bar) and after (black bar) SD. Error bars represent the standard errors.

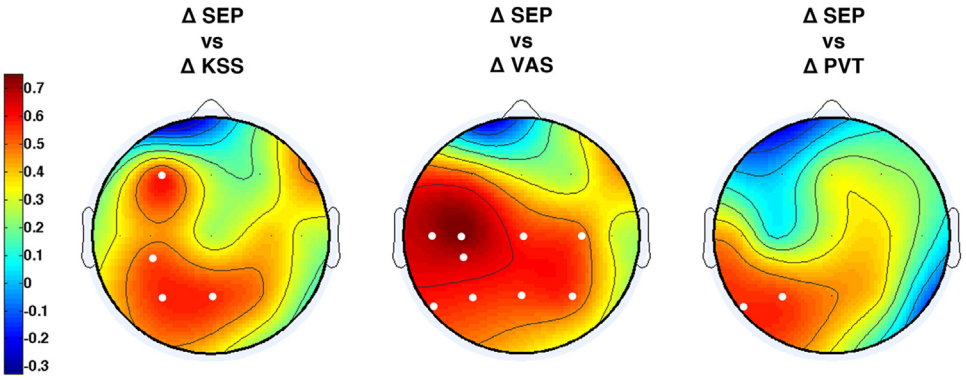

Figure 6. Topographic distribution of the Spearman's rank correlations coefficients ($n = 16$) between modifications after sleep deprivation (SD) of somatosensory evoked potentials (SEPs) voltage at 54 ms (ΔSEPs) and, respectively, post-SD changes of Karolinska Sleepiness Scale (ΔKSS), Visual Analog Scale for Global Vigor (ΔVAS) and Psychomotor Vigilance Task (ΔPVT). Values are expressed in terms of rho values: positive rho values indicate the presence of a positive correlation and vice-versa. The maps are based on 20 derivations (electrode positions indicated by dots). Values are color-coded and plotted at the corresponding position on the planar projection of the hemispheric scalp model. Values between electrodes were interpolated (biharmonic spline interpolation). The level of significance after False Discovery Rate (FDR) correction ($q \leq 0.03$; $P \leq 0.05$) corresponds to $\rho \geq 0.51$. Filled white circles indicate the electrodes with significant difference.

considered a good method to longitudinally evaluate cortical excitability in S1 cortex. A similar lack of effects of time of day on cortical responsiveness was observed also in human primary motor cortex [44] and in rat frontal and parietal cortex [22].

Changes in voltages scalp distribution after sleep loss

SD induced changes in the scalp distribution of voltages associated to SEPs following MN stimulation. In particular, a significant voltage increase was observed in the left occipital area at 35–43 ms and in fronto-central areas at 47–62 ms, indexing an enhancement of cortical responsiveness in both these cortical regions. The maximal voltage increase was observed at the Fz scalp location at 54 ms. Anterior areas are the most vulnerable to the negative effects of sleep loss [6]. The increase of EEG low-frequency bands after SD in fronto-central areas [8,9] is considered as a marker of the higher 'recovery need' of these regions. The increment of cortical responsiveness may represent another neurophysiological expression of the high 'recovery need' of the fronto-central areas after sleep loss. The higher voltage after SD at the occipital site is an unexpected result, more difficult to explain. A significant increase of occipital theta activity (although secondary to the frontal predominance) has been observed in human waking EEG after 40 h of prolonged wakefulness [8], indicating that this cortical region (secondarily to anterior areas) may be susceptible to the effects of sleep loss. Further studies are needed to clarify the possible relations between these phenomena.

An intriguing issue is the positive correlation observed between changes in cortical excitability and the expected increase of sleepiness with time awake, as assessed by self-rated (KSS and VAS) behavioral (PVT) measures. Scalp electrodes placed over (and in close proximity to) S1 area showed the highest positive correlations. These data, showing a site-specific link between cortical excitability and subjective measures of sleepiness, open new perspectives for the interpretation of the neurophysiological substrate of sleepiness, suggesting that the increased cortical excitability may be one of the mechanisms underlying the impairment in cognitive performance and alertness usually observed after prolonged wakefulness. Future studies will have to systematically investigate this relation.

Conclusions

The present study shows a clear enhancement of cortical excitability after SD as indexed by: (a) an amplitude increase of different SEPs component in S1; (b) higher voltage in occipital (around 35–43 ms) and fronto-central areas (around 47–62 ms). Circadian fluctuations do not seem to affect cortical excitability. Voltage changes in S1 were strongly related with post-SD fluctuation of subjective and behavioral sleepiness. These results suggest that sleep may have a role in keeping cortical excitability at optimal level (i.e., below potentially dangerous levels for the human brain), rebalancing changes in cortical responsiveness occurred during time spent awake. On the other hand, higher level of cortical responsiveness after sleep loss may be one of the mechanisms accounting for post-SD alterations in vigilance and behavior.

One limitation of this study concerns the topography of voltage changes associated to SEPs. The voltage scalp distribution associated with evoked potentials is affected by head volume conduction and by localization and orientation of the generators. Without any information concerning these issues, every interpretation about voltage topographical distribution remains speculative. Nevertheless, we believe that our data are informative, since a description of changes in voltage cortical distribution associated to SEPs after SD is, at present, not available in literature.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brs.2014.04.006.

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